the concentration of the drug that produces some standard biological effect, was related to its lipophilicity by the parabolic expression shown in Eq. (2.6).[41]

$$\log 1/C = -k(\log P)^2 + k'(\log P) + k'' \qquad (2.6)$$

On the basis of Eq. (2.5), it is apparent that if a compound is more soluble in water than in 1-octanol, P is less than 1, and, therefore, log P is negative. Conversely, a molecule more soluble in 1-octanol has a P value greater than 1, and log P is positive. The larger the value of P, the more there will be an interaction of the drug with the lipid phase (i.e., membranes). As P approaches infinity, the drug interaction will become so great that the drug will not be able to cross the aqueous phase, and it will localize in the first lipophilic phase with which it comes into contact. As P approaches zero, the drug will be so water soluble that it will not be capable of crossing the lipid phase and will localize in the aqueous phase. Somewhere between $P = 0$ and $P = \infty$, there will be a value of P such that drugs having this value will be least hindered in their journey through macromolecules to their site of action. This value is called log P_o, the optimum partition coefficient for biological activity.

This random walk analysis supports the parabolic relationship [Eq. (2.6)] between potency (log $1/C$) and log P (Fig. 2.4). Note the correlation of Fig. 2.4 with the generalization regarding homologous series of compounds (Section II,D,1; Fig. 2.1). An increase in the alkyl chain length increases the lipophilicity of the molecule; apparently, the log P_o generally occurs in the range of 5–9 carbon atoms. Hansch *et al.*[41] found that a number of series of nonspecific hypnotics had similar log P_o values, approximately 2, and they suggested that this is the value of log P_o needed for penetration into the central nervous system (CNS). If a hypnotic agent has a log P considerably different from 2, then its activity probably is derived from mechanisms other than just lipid

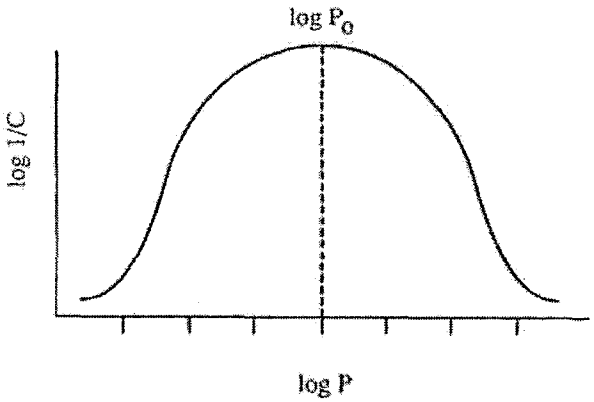


Figure 2.4. Effect of log P on biological response. P is the partition coefficient, and C is the concentration of the compound required to produce a standard biological effect.

transport. If a lead compound has modest CNS activity and has a log P value of 0, it would be reasonable to synthesize an analog with a higher log P.

Can you predict what analog will have a higher log P? In the same way that substituent constants were derived by Hammett for the electronic effects of atoms and groups (σ constants), Hansch and co-workers[29,37,39] derived substituent constants for the contribution of individual atoms and groups to the partition coefficient. The *lipophilicity substituent constant*, π, is defined by Eq. (2.7), which has the same derivation as the Hammett equation. The term P_X is the partition coefficient for the compound with substituent X, and P_H is the partition coefficient for the parent molecule (X = H). As in the case of the Hammett substituent constant σ, π is additive and constitutive. *Additive* means that multiple substituents exert an influence equal to the sum of the individual substituents. *Constitutive* indicates that the effect of a substituent may differ depending on the molecule to which it is attached or on its environment. Alkyl groups are some of the least constitutive. For example, methyl groups attached at the meta or para positions of 15 different benzene derivatives had π_{CH_3} values with a mean and standard derivation of 0.50 ± 0.04. Because of the additive nature of π values, π_{CH_2} can be determined as shown in Eq. (2.8), where the log P values are obtained from standard tables.[42] Because, by definition, $\pi_H = 0$, then $\pi_{CH_4} = \pi_{CH_3}$.

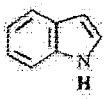
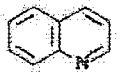
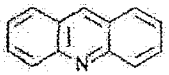
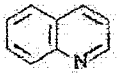
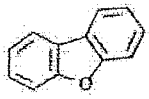
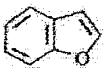
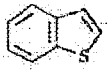
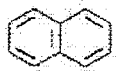
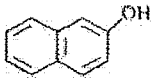
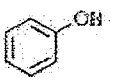
$$\pi = \log P_X - \log P_H = \log \frac{P_X}{P_H} \tag{2.7}$$

$$\begin{aligned} \pi_{CH_2} &= \log P_{\text{nitroethane}} - \log P_{\text{nitromethane}} \\ &= 0.18 - (-0.33) = 0.51 \end{aligned} \tag{2.8}$$

As was alluded to in Section II,D,2 on molecular modification, branching in an alkyl chain lowers the log P or π as a result of the larger molar volumes and shapes of branched compounds. As a rule of thumb, the value of log P or π is lowered by 0.2 unit per branch. For example, the $\pi_{i\text{-}Pr}$ value in 3-isopropylphenoxyacetic acid is 1.30; π_{Pr} is 3(0.5) = 1.50. Another case where π values are fairly constant is conjugated systems, as exemplified by $\pi_{CH=CHCH=CH}$ in Table 2.5.

Inductive effects are quite important to lipophilicity.[43] In general, electron-withdrawing groups increase π when a hydrogen-bonding group is involved. For example π_{CH_2OH} varies as a function of the proximity of an electron-withdrawing phenyl group [Eq. (2.9)],[44] and π_{NO_2} varies as a function of the inductive effect of the nitro group on the hydroxyl group [Eq. (2.10)].[43] The electron-withdrawing inductive effects of the phenyl group [Eq. (2.9)] and the nitro group [Eq. (2.10)] make the nonbonded electrons on the hydroxyl group less available for hydrogen bonding, thereby reducing the affinity of this functional group for the aqueous phase. This, then, increases the log P or π. Also

Table 2.5 Constancy of π for —CH=CH—CH=CH—[41,43]

Log P Difference					$\pi_{CH=CHCH=CH}$
log P 	— log P 	=	2.14 — 0.75 =	1.39	
log P 	— log P 	=	2.03 — 0.65 =	1.38	
log P 	— log P 	=	3.40 — 2.03 =	1.37	
log P 	— log P 	=	4.12 — 2.67 =	1.45	
log P 	— log P 	=	3.12 — 1.81 =	1.31	
log P 	— log P 	=	3.45 — 2.13 =	1.32	
2/3 log P 		=	2/3 (2.13) =	1.42	
log P 	— log P 	=	2.84 — 1.46 =	1.38	
			ave.	1.38 ± 0.046	

note in Eqs. (2.9) and (2.10) that, because $\pi_H = 0$ by definition, $\log P_{benzene} = \pi_{Ph}$.

$$\pi_{CH_2OH} = \log P_{Ph(CH_2)_2OH} - \log P_{PhCH_3} = -1.33$$
$$\pi_{CH_2OH} = \log P_{PhCH_2OH} - \log P_{PhH} = -1.03 \quad (2.9)$$

$$\pi_{NO_2} = \log P_{pHNO_2} - \log P_{PhH} = -0.28$$
$$\pi_{NO_2} = \log P_{p\text{-}NO_2PhCH_2OH} - \log P_{PhCH_2OH} = 0.11 \quad (2.10)$$

Resonance effects also are important to the lipophilicity much the same way as are inductive effects.[43] Delocalization of nonbonded electrons into aromatic systems decreases their availability for hydrogen bonding with the

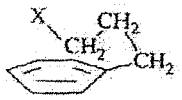
Table 2.6 Effect of Folding of Alkyl Chains on π[43]

X	π_X (aromatic)[a]	π_X (aliphatic)[b]	$\Delta\pi_X$
OH	−1.80	−1.16	0.64
F	−0.73	−0.17	0.56
Cl	−0.13	0.39	0.52
Br	0.04	0.60	0.56
I	0.22	1.00	0.78
COOH	−1.26	−0.67	0.59
CO_2CH_3	−0.91	−0.27	0.64
$COCH_3$	−1.26	−0.71	0.55
NH_2	−1.85	−1.19	0.66
CN	−1.47	−0.84	0.63
OCH_3	−0.98	−0.47	0.51
$CONH_2$	−2.28	−1.71	0.57
		Average	0.60 ± 0.05

[a] Log $P_{Ph(CH_2)_3X}$ − log $P_{Ph(CH_2)_3H}$.
[b] Log $P_{CH_3(CH_2)_3X}$ − log $P_{CH_3(CH_2)_3H}$.

aqueous phase and, therefore, increases the π. This is supported by the general trend that aromatic π_X values are greater than aliphatic π_X values, again emphasizing the constitutive nature of π and log P.

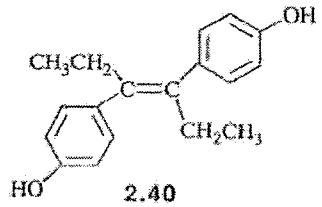
Steric effects are variable.[43] If a group sterically shields nonbonded electrons, then aqueous interactions will decrease, and the π value will increase. However, crowding of functional groups involved in hydrophobic interactions (see Chapter 3) will have the opposite effect. Conformational effects also can affect the π value.[43] The π_X values for $Ph(CH_2)_3X$ are consistently lower (more water soluble) than π_X values for $CH_3(CH_2)_3X$ (Table 2.6). This phenomenon is believed to be the result of folding of the side chain onto the phenyl ring (**2.39**), which means a smaller apolar surface for organic solvation. The folding may be caused by the interaction of the CH_2–X dipole with the phenyl π electrons and by intramolecular hydrophobic interactions.



2.39

Two examples follow to show the additivity of π constants in predicting log P values. A calculation of the log P for the anticancer drug diethylstilbestrol (**2.40**) is as follows:

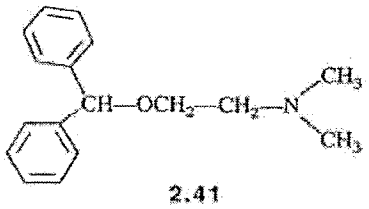
$$\begin{aligned} \text{Calc. log } P &= 2\pi_{CH_3} + 2\pi_{CH_2} + \pi_{CH=CH} + 2 \log P_{PhOH} - 0.40 \\ &= 2(0.50) + 2(0.50) + 0.69 + 2(1.46) - 0.40 \\ &= 5.21 \end{aligned} \qquad (2.11)$$



2.40

In Eq. (2.11), $\pi_{CH=CH} = \frac{1}{2}(\pi_{CH=CHCH=CH})$, which was shown in Table 2.5 to be $\frac{1}{2}(1.38)$; -0.40 is added into the equation to account for two branching points (each end of the alkene). The calculated log P value of 5.21 is quite remarkable considering that the experimental log P value is 5.07.

A calculation of log P for the antihistamine diphenhydramine (**2.41**) is shown in Eq. (2.12). In Eq. (2.12), 2.13 is log P for benzene, which is the same as π_{Ph}; 0.30 is $\pi_{CH_2}(0.50) - 0.20$ for branching; -0.73 was obtained by subtracting 1.50 $(2\pi_{CH_3} + \pi_{CH_2})$ from log $P_{CH_3CH_2OCH_2CH_3}$ $(=0.77)$; and -0.95 is the value for π_{NMe_2} obtained from $Ph(CH_2)_3NMe_2$.[43] The experimental log P value is 3.27.



2.41

$$\begin{aligned} \text{Calc. log } P &= 2\pi_{Ph} + \pi_{CH} + \pi_{COH_2} + \pi_{CH_2} + \pi_{NMe_2} \\ &= 2(2.13) + 0.30 - 0.73 + 0.50 - 0.95 \\ &= 3.38 \end{aligned} \qquad (2.12)$$

The chore of calculating log P values for molecules has been lessened considerably by the computerization of the method.[45] A nonlinear regression model for the estimation of partition coefficients was developed by Bodor *et al.*[46] using the following molecular descriptors: molecular surface, volume, weight, and charge densities. It was shown to have excellent predictive power for the estimation of log P for complex molecules.

Although the log P values determined from 1-octanol/water partitioning are excellent models for *in vivo* lipophilicity, it has been found for a variety of aromatic compounds with log P values exceeding 5.5 (very lipophilic) or molar volumes greater than 230 cm^3/mol that there is a breakdown in the correlation of these values with those determined from partitioning between L-α-phosphatidylcholine dimyristoyl membrane vesicles and water.[47] Above a log P value of 5.5 the solvent solubility for these molecules is greater than their membrane solubility. As the compound increases in size more energy per unit volume is required to form a cavity in the structured membrane

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